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Alkynyl Radicals, Myths and Realities

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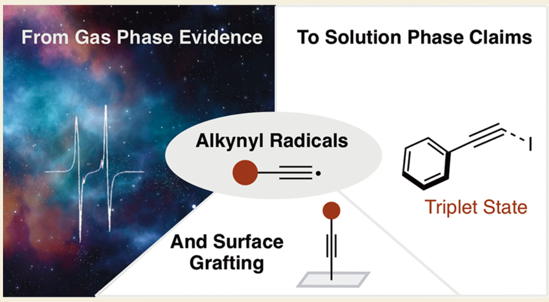
ABSTRACT: This Perspective deals with the organic chemistry of alkynyl radicals, a species that is ultimately still little known in the synthetic community. Starting with the first observations and characterizations of alkynyl radicals generated by various methodologies in the gas phase, we then particularly turned our attention to the implications of these highly reactive intermediates in organic synthesis and materials science. Mechanistic considerations have been provided, in particular, for the key steps of generating alkynyl radicals, which are mainly based on photochemical or thermal activation and single electron transfer processes. This Perspective should serve as a roadmap for the synthetic chemist in order to plan more reliably alkynylation reactions based on alkynyl radicals.



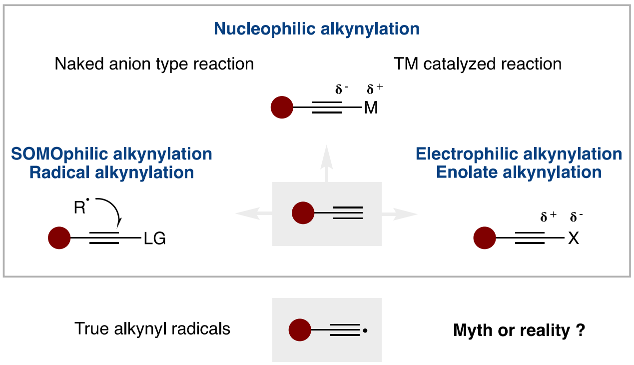
KEYWORDS: *alkynyl radical, radical chemistry, photochemistry, energy transfer, alkynyl halides, SET*

INTRODUCTION

Alkynyl groups, well-appreciated for their rigidity, linearity, and hydrophobicity,[1] have experienced a surge in popularity over the past few decades as versatile building blocks in synthetic organic chemistry for the synthesis of complex pharmaceutical molecules and in materials science.[2,3] They have also found applications as bioorthogonal tags for click reactions,[2] enabling selective labeling and imaging of biomolecules. Traditionally, the introduction of an alkyne group to molecules has been achieved through nucleophilic pathways by employing metal acetylides or by using transition metal catalysts (Sonogashira coupling)[4,5] or via electrophilic alkynylation (Scheme 1).[6] In the latter method, the carbon of the alkynyl group acts as the electrophile in the presence of nucleophiles, such as enolates, offering an alternative strategy for alkyne incorporation.

The development of radical alkynylation, where a radical is added to an alkynyl precursor via an α-addition/β-elimination sequence, also known as SOMOphilic alkynylation, has offered an alternative to these conventional approaches.[7] This methodology, which relies on the use of various radical precursors, most notably ethynylbenziodoxolones (EBX),[7] allows for milder reaction conditions, greater functional group tolerance, and higher yields with excellent selectivity. Moreover, it offers the ability to run radical cyclization cascades, which is potentially useful in the synthesis of pharmaceutical targets. Despite the utility of this methodology, it does not directly address the formation of genuine alkynyl radicals, which could prove to be even more valuable synthons in organic synthesis. C-centered radicals, particularly alkyl,[8] alkenyl,[9] and aryl radicals,[10] have been extensively studied and documented in the literature. In stark contrast, alkynyl radicals have remained relatively elusive in the scientific literature. This paucity of reports on alkynyl radicals primarily stems from the challenges associated with their generation and unique properties. In this Perspective, we will focus on methods involving the direct formation of alkynyl radicals. Our objective is to highlight the works that mention the involvement of these radical or radical-like species through mechanistic studies. Therefore, we will not discuss the previously mentioned SOMOphilic alkynylation and its scope, as these have been thoroughly reviewed by Waser.[7,11] By doing so, we aim to provide a comprehensive examination of alkynyl radicals covering their sources, properties, and synthetic applications. The Perspective is structured into three sections.

Scheme 1. Typical Alkynylation Pathways



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The first one will present early works confirming the observation of alkynyl radicals, discuss their properties, and explore the methods by which they could be generated as well as their reactivity in the gas phase. This section provides a foundational understanding of alkynyl radicals and their unique characteristics. The second section will focus on the body of work in the condensed phase concerning the potential involvement of alkynyl radicals for organic synthesis, categorized according to the source of the alkynyl radical intermediates: alkynyl halides (the most widely used precursors) and alkynylsulfonium salts and sulfones as well as metal acetylides. Several methodologies will be discussed including direct UV irradiation, photosensitization (energy transfer, EnT), reductive or oxidative single electron transfer (SET), or thermal activation. The third section covers the application of some of these methodologies for the grafting of alkynyl radicals onto surfaces. Finally, faced with a sometimes disconcerting literature, a re-evaluation of the generation of alkynyl radicals and their authentication is addressed in a fourth section.

■ ALKYNYL RADICALS: EARLY REPORTS, CHARACTERIZATION, AND PROPERTIES

When alkynyl radicals are considered, the ethynyl radical is perhaps the most prominent example that comes to mind. As the simplest alkynyl species, it plays an important role in complex environments such as high-temperature combustion flames and low-temperature interstellar media.[12−18] Cochran, Adrian, and Bowers were the first to directly detect and characterize the ethynyl radical in 1964 through an electron paramagnetic resonance (EPR) spectroscopy study.[19] They generated this reactive intermediate by ultraviolet photolysis of acetylene trapped in an inert solid argon matrix.

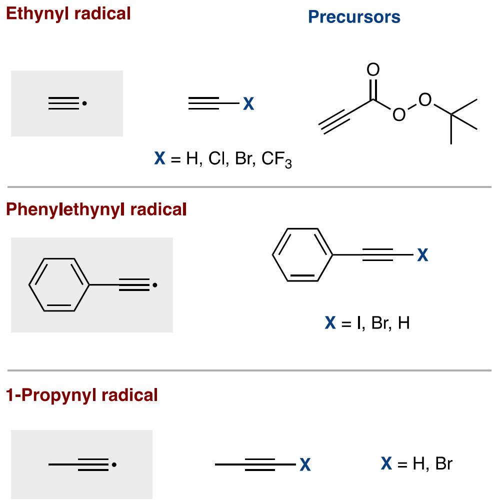
Phenylethynyl radical can be considered a more stable example of alkynyl radicals compared to the ethynyl radical.[20] Although it is present less than its ethynyl counterpart in interstellar environments,[21,22] the phenylethynyl radical is much more relevant from a synthetic point of view. Even rarer than the phenylethynyl radical is the 1-propynyl radical, though its presence has also been detected in space, and it is considered an important reactant in hydrocarbon-rich interstellar systems.[23] Despite the pronounced structural similarity among phenylethynyl, 1-propynyl, and ethynyl radicals, they possess different properties, which will be discussed hereafter.

Formation and Properties

The abundance of alkynyl radicals in cosmic environments can be attributed to the relative ease with which the alkynyl C−H bond can undergo photolysis initiated by ultraviolet radiation from nearby stars.[24,25] Therefore, most of the initial efforts to access these radicals rely on the photodissociation of the corresponding alkynes. It is crucial to note that this requires specialized experimental setups. One approach involves trapping the radical species in solid noble gas matrices at cryogenic temperatures,[19] while the other approach relies on the use of a crossed molecular beams machine under single-collision conditions in the gas phase at very low pressures.[26] Under single-collision conditions, particles from one beam collide once with particles from another beam or are photolyzed by a laser beam. The resulting reaction products are then detected using various spectroscopic methods. This approach allows for the study of elementary reaction steps without interference from secondary collisions.[27]

If we take the ethynyl radical, it was successfully formed starting from acetylene precursors (Scheme 2);[19,28,29] however, the photodissociation pathway is not as simple as it seems as was shown by Cui and Morokuma.[30] Halogenated acetylenes were also used as a source of ethynyl radical under photolysis conditions but are not considered ideal precursors due to their instability and risk of polymerization.[31−33] The use of 3,3,3-trifluoropropyne ($CF_3C{\equiv}CH$) showed a huge potential as an alternative precursor.[34] Upon irradiation at 190 nm, the compound fragments, yielding the desired ethynyl radical alongside the more stable CF_3 radical. This clean fragmentation of $CF_3C{\equiv}CH$ makes this alkyne a privileged precursor for generating ethynyl radicals.[35] Peroxides were also considered as a source of ethynyl radicals (Scheme 2) under flash pyrolytic conditions, but they have remained less explored.[36]

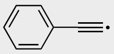
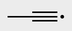
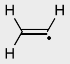
Scheme 2. Diverse Precursors Used in the Formation of Alkynyl Radicals under Photolysis or Pyrolysis Conditions



Contrary to the logical assumption that a simple photodissociation of phenylacetylene could lead to the formation of the corresponding phenylethynyl radical, the clean formation of this species has appeared to be much more tricky. The pyrolysis of phenylacetylenes led to various reactive species including phenyl radicals.[37,38] The phenylethynyl radical was observed alongside the *ortho*-, *meta*-, and *para*-ethynylphenyl radical isomers ($HC{\equiv}CC_6H_4\cdot$), which are easier to form than the acetylenic radical. The easiest way to access phenylethynyl radicals is through the photolysis of phenyliodoacetylene, as reported by Walton and co-workers,[20] and this is considered the standard way to form these radicals, as seen in all posterior works studying this radical species.[39] The same can be said for phenylbromoacetylene, as it served the same purpose as phenyliodoacetylene for facilitating access to phenylethynyl radicals.[40]

Building upon the work on ethynyl and phenylethynyl radicals, investigations into the generation of other simpler alkynyl radicals were undertaken. In particular, the formation of propynyl radicals has become a subject of interest. Initially, it was believed that a simple photolysis of propyne at 193 nm would cleanly lead to the formation of 1-propynyl radical.[41] However, later studies showed that excitation of propyne at 157 nm produces a 73:27 mixture of 1-propynyl and propargyl radicals.[42] Similar results were observed by Ashfold's group, where the selectivity was highly dependent on the irradiation

Table 1. Comparison of Three Different Alkynyl Radicals and the Vinyl Radical[a]

Radical	Ethynyl	Phenylethynyl	1-Propynyl	Vinyl
				
Nature	σ radical	π radical	non bonding σ, π radical ?	σ radical
BDE (kcal.mol^{-1})	131.74 [33]	128.8 [45]	130.2 ± 3 [48]	110.2 [50]
I.P (eV)	11.6 ± 0.5 [52]	–	13.11 ± 0.09 [51]	8.25 ± 0.2 [53]
E.A (eV)	2.969 ± 0.006 [55]	3.03 [45]	2.7355 ± 0.0010 [51]	0.6678 [56]
g tensor	2.0025 ± 0.0005 [28]	2.0030 ± 0.0003 [39]	–	–

[a] BDE (kcal·mol^{-1}): Bond dissociation energy. IP (eV): Ionization Potential. EA (eV): Electron Affinity. g-tensor: Magnetic moment interaction.

wavelength.[43] At 121.6 nm, there are two competing pathways for H atom formation: a faster channel leading to 1-propynyl radical and a slower channel likely forming the propargyl radical. For the 193.3 nm photolysis of propyne, the consensus is that the C_3H_3· fragment is likely predominantly the propargyl radical. A direct way to get the 1-propynyl radical is through photodissociation of 1-bromopropyne.[44]

To better understand the stability and reactivity of ethynyl, phenylethynyl, and 1-propynyl radicals, we summarized their different properties in Table 1. In the case of phenylethynyl, it has been characterized as a π radical in both gas phase and solution phase studies.[39,20] This was demonstrated by the work of Kasai and McBay, where they showed that the σ and π electronic states undergo mixing and crossing due to the interaction between the π_z orbital of the ethynyl moiety and the E_{1a} π orbital of the phenyl group.[39] The antisymmetric orbital interaction produces the highest occupied semifilled molecular orbital (SOMO), which has a π character and is less stable than the nonbonding σ orbital localized on the ethynyl moiety.

Various Density Functional Theory (DFT) methods support this conclusion.[45] This contrasts with the ethynyl radical, which is described as σ radical.[28,46] For the 1-propynyl radical, however, theoretical studies showed that the unpaired electron was on a nonbonding σ orbital;[47−49] but, the π state of this radical was shown to be an extremely low lying excited state, which makes it easier to access a π like radical character.

The difficulties associated with the formation, stability, and reactivity of these radicals can be understood by looking at key thermodynamic and kinetic parameters, notably, the bond dissociation energy (BDE) values (Table 1). The BDE values for the three reported alkynyl radicals are notably similar, with the phenylethynyl radical exhibiting a slightly lower BDE compared to the 1-propynyl and ethynyl radicals. This subtle difference may be attributed to the stabilizing effect of the phenyl moiety on the radical.[15,33] Alkynyl radicals are characterized by high BDE values of approximately 130 kcal·mol^{-1}, which is about 20 kcal·mol^{-1} higher than those of vinyl radicals.[50] This substantial energetic difference explains why the generation of alkynyl radicals is particularly challenging under the standard conditions. In fact, alkynyl radicals are among the most difficult radical species to form, necessitating conditions that provide sufficient energy to overcome these considerable barriers. Ionization potentials (IPs) were evaluated. 1-Propynyl radical has a higher IP of 13.11 eV compared to the ethynyl radical, making the 1-propynyl radical more difficult to ionize.[51,52] Unsurprisingly, the IP values for alkynyl radicals are higher compared to vinyl radicals.[53,54] In addition, due to the resonance stabilization by the phenyl group, the phenylethynyl radical has the highest electron affinity (EA) of 3.03 eV out of the three radicals,[45] and the EA of 1-propynyl radical is slightly lower than that of the ethynyl radical, indicating a lesser tendency to accept an electron.[51] Therefore, the ethynyl radical falls between these extremes, with a high ionization potential and moderate electron affinity.[55] When compared with the vinyl radical, which has an EA value of 0.6678 eV,[56] these alkynyl radicals clearly show a higher tendency to accept electrons. Two of these radicals were isolated and trapped in a solid matrix; they were analyzed by EPR,[19] and their g tensor values were measured.[28,39] Table 1 thus provides valuable insights into the stability and reactivity of the alkynyl radicals in general and of ethynyl, phenylethynyl, and 1-propynyl radicals in particular.

Another crucial parameter that characterizes radical species and aids in predicting their reactivity and selectivity in various transformations is their polarity. Radical polarity is typically described in terms of nucleophilicity or electrophilicity, which are kinetic concepts rather than thermodynamic parameters. Recently, Nagib and co-workers conducted a comprehensive theoretical study on the polarity of a large pool of radicals, which was subsequently validated experimentally.[57] They found that alkynyl radicals, along with nitrile radicals, were among the most electrophilic of the 500 examples studied. Due to their strong electrophilic character (ω = 3.37 eV for the alkynyl radical vs 1.25 eV for the vinyl radical), which is consistent with their high EA, alkynyl radicals are expected to be highly reactive under various conditions. Notably, they should readily abstract hydrogen atoms from other molecules present in a reaction mixture (a process known as hydrogen atom transfer or HAT). In the presence of electron-rich π systems, these radicals would also readily undergo addition reactions. This pronounced electrophilicity explains the challenges associated with handling these radicals, particularly in solution.

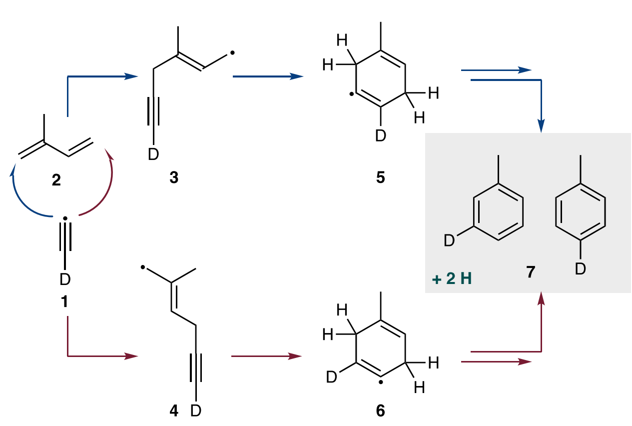
Reactivity in the Gas Phase

Given the highly reactive nature of alkynyl radicals, they could easily be engaged in various transformations. Taking the combustion process as a case study, the ethynyl radical was formed through hydrogen atom abstraction of acetylene.[58] The presence of oxygen in the medium leads to the formation of various products through diverse pathways, with the most exothermically favorable pathways giving rise to four major products: carbon monoxide (CO), formyl radical (HCO·), ketenyl radical (HCCO·), and atomic oxygen (O).[59,60] Detailed experimental and theoretical studies have been conducted to elucidate the diverse mechanisms through which these products are formed, highlighting the key intermediates and transition states involved.[61] The prevailing consensus is that the reaction proceeds via an initial barrierless formation of the ethynyl peroxy radical (HCCOO·), which subsequently branches into multiple reactional pathways.

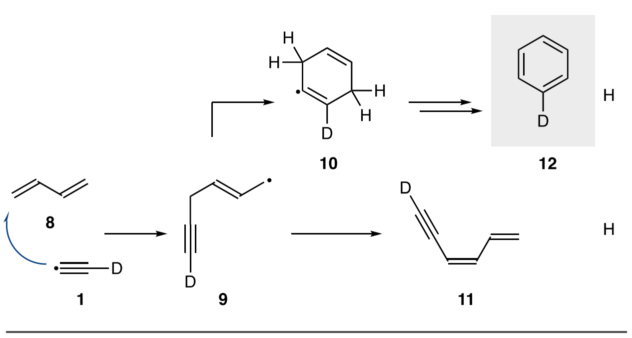
Aside from their reactivity with oxygen, D-ethynyl radicals **1** were found to react with isoprene **2** in a single collision event in the gas phase, leading to the formation of toluenes **7** and atomic hydrogen. Toluene is considered a building block of polycyclic aromatic hydrocarbons (PAHs) species in interstellar space. This study rationalizes the presence of light aromatic derivatives like toluene in both high-temperature combustion flames and low-temperature interstellar media.[62,63] When D-ethynyl radical reacts with isoprene, it encounters two possibilities: addition to either the C1 or C4 carbon atoms (Scheme 3a), resulting in four intermediates that ultimately decompose into six noncyclic reaction products in an overall exoergic process.[64] Two of these intermediates (**3** and **4**) can isomerize through ring closures, forming **5** and **6** (Scheme 3a), which can then readily undergo hydrogen shifts followed by hydrogen atom loss, ultimately producing toluene **7** in an exoergic reaction with computed energetics of 88.5 kcal·mol^{-1}, remarkably consistent with the experimental value of 88.3 kcal·mol^{-1}.

Scheme 3. (a) Reactivity of Ethynyl Radical with Isoprene; (b) Reactivity of Ethynyl Radical with 1,3-Butadiene

a. Reactivity of ethynyl radical with isoprene



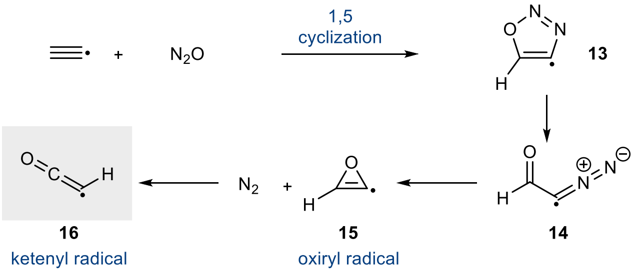
b. Reactivity of ethynyl radical with 1,3-butadiene



A related study by Jones et al. on the reaction of D-ethynyl **1** radical with 1,3-butadiene **8** and its deuterated analogues depicts the role of ethynyl in the formation of aromatic molecules with a benzene core through a barrierless process in cold molecular clouds (Scheme 3b).[65] The reaction proceeds through the addition of the ethynyl radical to a terminal carbon center of 1,3-butadiene to give intermediate **9**. This intermediate can either evolve to form 1,3-hexadien-5-yne isomer **11** or cyclize to give intermediate **10**. The latter undergoes a hydrogen shift, followed by the loss of a single hydrogen atom, forming benzene-d_1. Under conditions similar to those in cold molecular clouds (low temperatures around 10 K), about 40% of the products formed are benzene. This study provides evidence of a plausible low-temperature route for benzene formation in space, which has implications for understanding the origins of more complex PAH species and organic molecules in the universe.

The reaction between the ethynyl radical (C_2H·) and nitrous oxide (N_2O) has been investigated both experimentally and theoretically.[66] This reaction primarily occurs at elevated temperatures, and the study revealed that the most favored process involves the addition of a C-centered radical to the terminal nitrogen of nitrous oxide (Scheme 4). By proceeding through a five-membered cyclic intermediate **13**, followed by ring opening to **14**, the ketenyl radical **16** (HCCO·) is ultimately formed via elimination of N_2 and the rapid rearrangement of the highly reactive oxiryl radical **15** to its most stable isomer **16**. The channel leading to HCNN· + CO was shown to be the other most likely, albeit minor, pathway that could arise from this reaction.

Scheme 4. Addition Channels of C_2H and N_2O Reaction

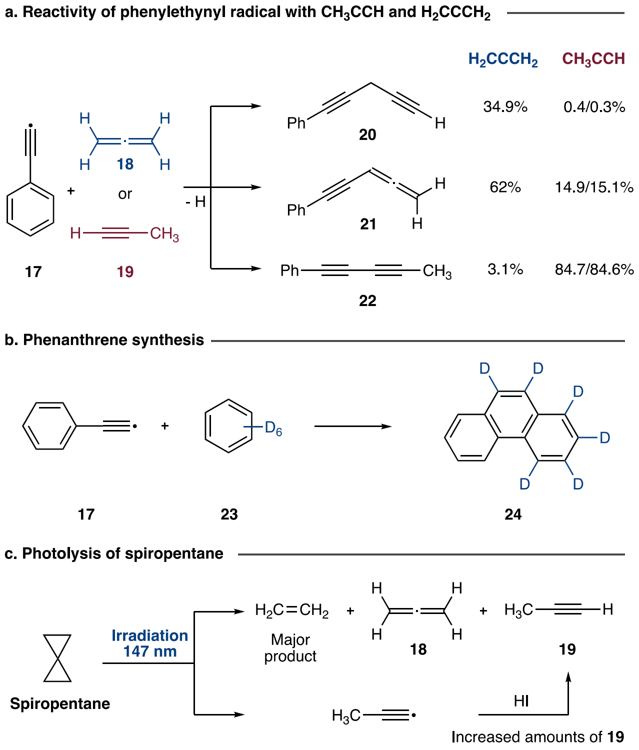


The reactivity of the ethynyl radical has been extensively studied, beyond the scope of this work. While a comprehensive review is not provided here, we direct interested readers to the substantial body of literature on this topic.[67−70]

In contrast, the reactivity of the phenylethynyl radical is much less studied. A recent study explored the involvement of phenylethynyl radical **17** in the molecular mass growth processes, combining experimental gas-phase studies using crossed molecular beams with theoretical electronic structure calculations.[71] The results showed that reactions of the phenylethynyl radical **17** with allene **18** (H_2CCCH_2) and methylacetylene **19** (CH_3CCH) lead to three similar products but with different branching ratios (Scheme 5a). In the case of the phenylethynyl-allene system, the radical can attack either the terminal carbon of the allene **18** or the central one, and the latter can isomerize to form 1,4-pentadiyn-1-ylbenzene **20** and 3,4-pentadien-1-yn-1-ylbenzene **21** through an addition−elimination pathway in an overall exoergic process. However, the formation of 1-phenyl-1,3-pentadiyne **22** requires further isomerization steps, which explains why the branching ratios favor **21** (**20**: 34.9%; **21**: 62%; **22**: 3.1%). The phenylethynyl-methylacetylene system favors the formation of compound **22** as the major product, likely due to a simpler reaction mechanism (direct addition−elimination). The branching ratios for this system reflect this reactivity, with compound **22** obtained in 84.7/84.6%, **20** in 0.4/0.3%, and **21** in 14.9/15.1%.

The bimolecular gas-phase reaction of the phenylethynyl radical **17** with deuterated benzene **23** was shown to lead to the

Scheme 5. (a) Major Product Channels from the Reactions of Methyl-Acetylene (CH_3CCH) and Allene (H_2CCCH_2) with Phenylethynyl Radical; (b) Phenanthrene Synthesis from Phenylethynyl Radical; (c) Photolysis of Spiropentane



formation of phenanthrene through unconventional excited state dynamics.[40] This reaction is initiated by the barrierless addition of a phenylethynyl radical to benzene-*d*, followed by deuterium migration (Scheme 5b). The global reaction mechanism involves multiple deuterium/hydrogen migrations and ring opening/closing isomerizations before finally yielding phenanthrene **24** via atomic hydrogen loss. This mechanism is specific to phenylethynyl radical and benzene; when phenyl radical reacts with phenylacetylene, cyclization to phenanthrene does not occur.

The study of 1-propynyl radicals has been less frequent due to challenges in their generation, limiting investigations into their roles in hydrocarbon growth mechanisms. Nevertheless, the reaction between 1-propynyl radical and acetylene was studied under single collision conditions, leading to the formation of C_5H_4 isomers.[72] Analysis of the products formed out of this reaction revealed that the main product was methyldiacetylene (CH_3CCCCH) plus atomic hydrogen. Similar results were obtained when ethynyl radical reacts with acetylene, producing diacetylene (HCCCCH), suggesting that 1-propynyl radical reactivity closely resembles that of the ethynyl radical. 1-Propynyl radical reacted also with benzene, yielding 1-phenyl-1-propyne product ($C_6H_5CCCH_3$) as the main product alongside atomic hydrogen.[73] This reaction was shown to proceed through a barrierless addition of the 1-propynyl radical to benzene, following a simple addition/elimination mechanism.

In 1985, Paller and Doepker reported an intriguing study on the generation of 1-propynyl radicals.[74] They investigated the gas-phase photolysis of spiropentane by using xenon resonance radiation at 147.0 nm (Scheme 5c). The major products identified were ethylene, allene **18**, and propyne **19**, with ethylene being the most abundant. A key observation was the increase in the propyne yield when HI (hydrogen iodide) was added to the reaction mixture. Importantly, this increase was not accompanied by an increase in allene production. This selectivity ruled out the involvement of propargyl radicals in this reaction channel, as propargyl radicals would have led to increases in yields for both **18** and **19**. Instead, the selective increase in propyne strongly suggested the presence of 1-propynyl radicals that are intercepted by HI to form methylacetylene exclusively.

Overall, alkynyl radicals play an important role in various chemical processes with significant implications for our understanding of cosmic chemistry. These species are key players in forming complex molecules such as polycyclic aromatic hydrocarbons (PAHs). Further understanding of the mechanisms involved will help to elucidate the chemical evolution of the universe, from probing remote star characteristics to the possibility of extraterrestrial life.

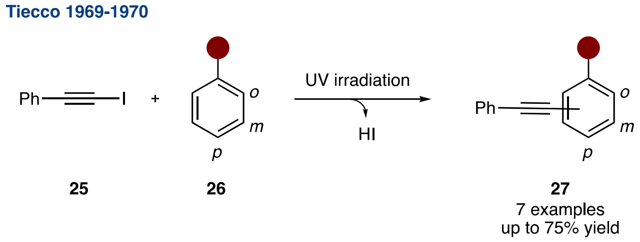
■ ALKYNYL RADICALS AS PUTATIVE INTERMEDIATES IN ORGANIC SYNTHESIS

Alkynyl Halides and Congeners as Precursors

A series of alkynylation reactions in the condensed phase mentioning alkynyl radicals as intermediates has emerged over the past decades. The majority of them relied on alkynyl halides as precursors exposed to light or thermal activation. In some reports, the intervention of a genuine alkynyl radical remains dubious, and this is why we used the term "putative" in the title of this section. Nevertheless, we decided to cover all the reports featuring an alkynyl radical intermediate and evidence of the alkynyl radical formation were addressed where possible.

Direct UV Irradiation. In the very late 1960s, the Tiecco group reported a series of findings dealing with the involvement of the phenylethynyl radical in homolytic aromatic substitution reactions on aryl derivatives. While the thermolysis of phenylpropiolyl peroxide proved to be inefficient for the generation of the phenylethynyl radical, the authors took inspiration from the photolysis of iodo aromatic compounds and engaged 1-iodo-2-phenylacetylene **25** as precursor under UV irradiation (Scheme 6). When conducted in benzene, this photolysis reaction yielded diphenylacetylene in 75% yield. Competitive experiments revealed that other alkylbenzene derivatives including toluene, ethylbenzene, cumene, and *tert*-butylbenzene exhibited higher reactivity than benzene when used as solvents. In the cases of toluene, *p*-xylene, and mesitylene, a competing hydrogen atom transfer (HAT) mechanism was proposed to explain the formation of benzyl iodide, *p*-methylbenzyl iodide, and 3,5-dimethylbenzyl iodide, respectively. However, the yields of these iodide products were not quantified. While *ortho*-, *meta*-, and *para*-regioisomers of 1-

Scheme 6. Homolytic Aromatic Substitution by Phenyethynyl Radicals



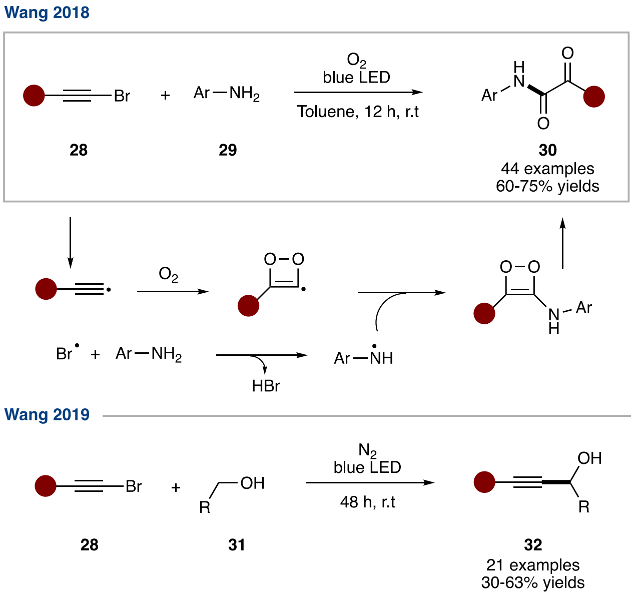
aryl-2-phenyl-acetylenes **27** were obtained, a higher percentage of ortho-substitution than with sp^3 or sp^2 radicals was observed due to less steric constraint.[75] The higher electrophilic character of the phenylethynyl radical was evidenced by the fact that a higher *para*-orientation was observed than with the phenyl radical. Also, halogenobenzenes showed an attenuated reactivity toward the phenylethynyl radical.[76]

In 1982, Inoue's group observed that, upon irradiation at wavelengths above 200 nm, 1-bromo-1-hexyne and 1-iodo-1-hexyne undergo homolytic cleavage of the C−X bond (C−Br or C−I), resulting in the formation of the 1-hexynyl radical.[77] They claimed that the inability to generate ionic products, even in polar solvents, provides strong evidence of the radical nature of the photolysis of these compounds. This conclusion was further supported by UV absorption experiments and by the high IP of alkynyl radicals as discussed before, which makes the formation of 1-hexynyl cations energetically unfavorable, explaining the absence of ionic behavior in these reactions.

Blue LED Activation. The recent development of LED devices has favored the development of photochemical processes under milder conditions than UV irradiations. Several recent reports have dealt with the putative involvement of alkynyl radicals under these irradiation conditions.

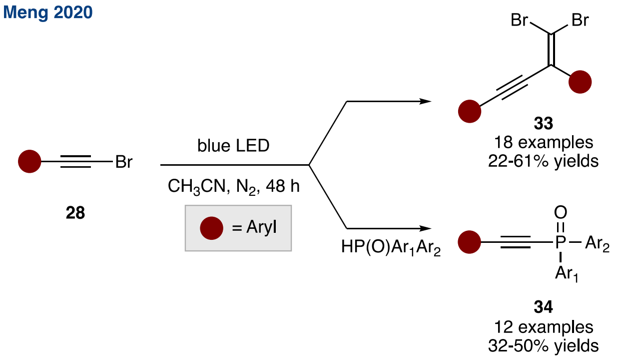
Thus, 1-bromoalkynes **28** could be coupled to anilines **29** under blue LED irradiation and an oxygen atmosphere to produce bis-aryl-α-ketoamides **30**.[78] Initial formation of an alkynyl radical intermediate through blue LED irradiation was proposed, notably based on the detection by GC/MS of the corresponding diyne species. This alkynyl radical would be trapped by oxygen, followed by a final radical−radical[79,80] coupling with the somehow persistent aniline radical species (Scheme 7). The presence of singlet dioxygen was excluded in this reaction. Based on this work, the same group reported the coupling of bromoalkynes **28** with alcohols **31** as reagents and solvents under similar conditions (Scheme 7).[81] Interestingly, under an oxygen atmosphere, the corresponding α-ketoester derivatives could be obtained as before, while under a N$_2$ atmosphere propargyl alcohols **32** were formed, presumably via H-abstraction at the α-position to the oxygen atom of the alcohols **31** and radical combination of the resulting radical with the alkynyl radical. Similar alkynylation of α-C−H bonds of ethers was reported using the ether partner (THF, diethyl ether, dioxane, etc.) and KF as a base under blue LED irradiation.[82]

Scheme 7. Photoinduced Alkynylation of Amines and Alcohols



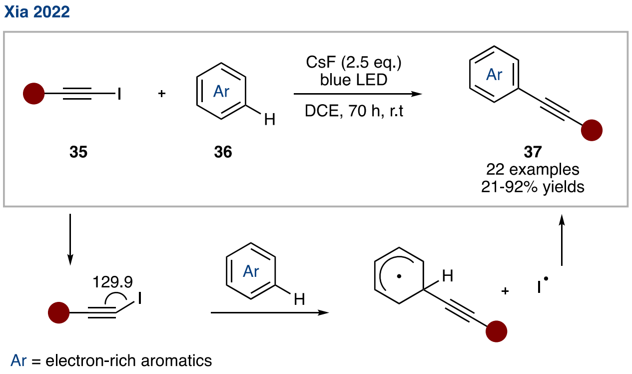
The Meng group studied the visible light-promoted head-to-tail dimerization of bromo-arylalkynes **28** to furnish 1,1-dibromo-1-en-3-yne derivatives **33**,[83] a type of compound previously observed as side product in the reaction of bromoalkynes and alcohols (Scheme 8).[81] The yield of **33** with aryl = phenyl could be improved to 61% by adjusting the wavelength of the blue LEDs and prolonging reaction time for 48 h in MeCN. Having in mind that the Br· radical could abstract hydrogen from secondary phosphine oxides, a C−P coupling process was also devised to provide access to alkynylphosphine oxides **34**.[83]

Scheme 8. Photoinduced Head to Tail Coupling of Bromoalkynes



The works of Xia's group dealing with the photoinduced alkynylation of aromatic rings, formally consisting of a metal-free inverse Sonogashira coupling, provided more insight into the possible involvement of alkynyl radical species (Scheme 9).[84]

Scheme 9. Photoinduced Inverse Sonogashira Reaction

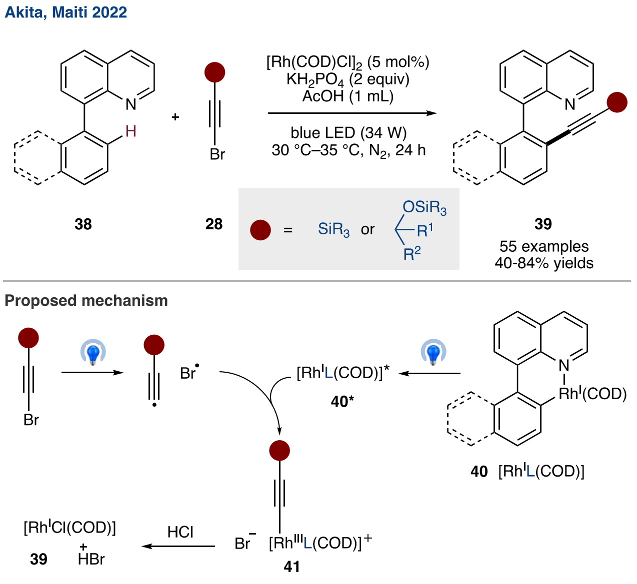


Experimentally, the iodoalkyne partner **35** was opposed to an excess (25 equiv) of arene and heteroarene derivative **36** in the presence of 2.5 equiv of CsF, which was also found to be the most competent base. This mixture was irradiated under very high power blue LEDs (2 × 90 W Kessil lamps) for a prolonged reaction time (70 h). Best yields were obtained with electron-rich partners. Theoretical calculations allowed the identification of an excited state resulting from the irradiation and resembling the modeled triplet excited state of the iodoalkyne partner featuring a bent structure[85] (C−C−I angle of 130°, C−I = 2.20

Å vs 2.01 Å in the ground state). This species can be regarded as an "alkynyl radical synthetic equivalent" that easily reaches with a barrier of 3.2 kcal·mol^{-1} the transition state of a concerted nucleophilic addition to benzene and release of the iodine radical. The resulting adducts then undergo oxidation and deprotonation. The alkynyl radical reactivity was also supported by spin trapping experiments with TEMPO and the nitrone derivative 5,5-dimethyl-1-pyrroline N-oxide (DMPO), and the adducts were characterized by low resolution MS. In the case of the DMPO trapping, an EPR spectrum was provided.

In 2022, the groups of Akita and Maiti reported a quite intriguing example of organometallic catalysis driven by the photoactivation of an organometallic intermediate[86] that both serves as nexus for the C−C bond formation and as light harvesting antenna (Scheme 10).[87] More specifically, a photoexcited rhodacycle **40** stemming from a C−H activation process of 2-phenyl pyridine substrates **38** would react through two-electron transfers with an alkynyl radical presumably originating from a high power (34W) blue LED-promoted homolysis of the alkynyl bromide partner **28**. The resulting alkynylated rhodium(III) metallacycle **41** undergoes reductive elimination to liberate ortho-alkynylation arene products **39**.

Scheme 10. Rh Catalyzed Photoinduced Ortho-Alkynylation

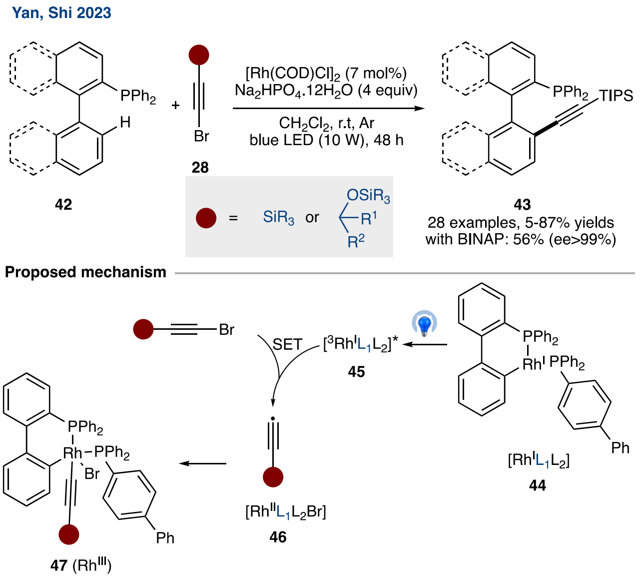


Evidences on the intervention of an alkynyl radical were based on the HRMS detection of the TEMPO trapping adduct as well as the formation of the diyne side-product. Such a mild temperature (35 °C) pathway obviates the typical harsh conditions of thermally induced C−H activation processes and, notably, the use of exogenous oxidants.

A related orthoalkynylation of biaryl-type phosphines **42** with TIPS-alkynyl bromides **28** and similar rhodium catalysis, employing the phosphorus center as directing groups, has been recently reported (Scheme 11).[88] A broad scope of substrates **43** has been obtained, including the optically pure bis-naphthyl derivative.

DFT calculations suggest that, under light irradiation, rhodacycle **44** undergoes photoexcitation to reach the triplet state **45** prone to promote the homolysis of the alkynyl bromide partner by SET. The system would evolve to rhodium(II)-bromide complex **46**. The latter then intercepts the alkynyl radical to form Rh(III) complex **47**, which undergoes reductive elimination with an activation barrier of 9.1 kcal·mol^{-1}. The proposal for the intervention of an alkynyl radical was based on the EPR of a spin-trapping adduct with DMPO.

Scheme 11. Photoinduced Rh Catalyzed P(III)-Directed C−H Activation



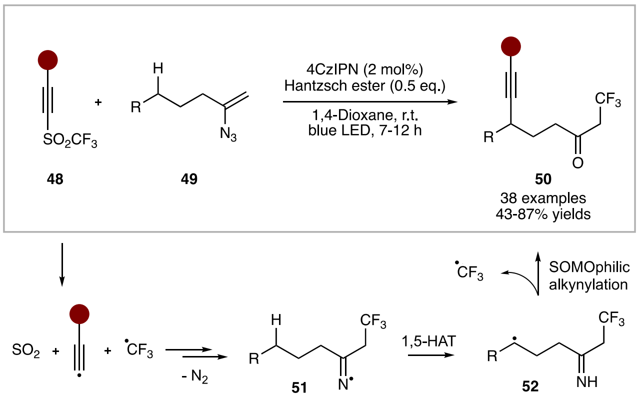
Blue LED Promoted Energy Transfer (EnT) Processes. Other reports have converged on the fact that the generation of an alkynyl radical can be generated through EnT from a photoexcited species in the reaction medium. For instance, a report by Li, Ma, Chen, and co-workers showed that in their conditions of irradiation by 9 W blue LEDs under air the Fukuzumi acridinium photocatalyst (10-methyl-9-(2,4,6-trimethylphenyl)acridinium perchlorate) was required to obtain the previously mentioned 1,1-dibromo-1-en-3-yne derivatives **33** from the corresponding bromoalkynes.[89] EnT transfer from the photoexcited acridium was invoked to promote the homolytic C−Br bond cleavage, but no luminescence quenching was mentioned to support this hypothesis.

A more documented case of EnT was provided by Lin, Liu, and Liu in a study based on the use of alkynyl triflones **48** as radical precursors and 4CzIPN as photocatalyst to yield a C(sp3)−H alkynylation of vinyl azides **49**.[90] Based on luminescence quenching studies, they demonstrated that, under an EnT and not a SET process, alkynyl triflones **48** are cleaved homolytically, liberating a trifluoromethyl radical and the alkynyl radical that would be hydrogenated by the Hantzsch ester. A TEMPO trapping adduct of an alkynyl radical was characterized by HRMS and showed the correct exact mass. Following the addition of the trifluoromethyl radical onto the vinyl moiety of **49**, loss of N$_2$ generates an iminyl radical **51** that undergoes 1,5-HAT to provide a more stabilized alkyl radical **52**. After SOMOphilic alkynylation to give final alkynylated products **50**, a new trifluoromethyl radical is eliminated and sustains a radical chain (Scheme 12). A quantum yield determination gave a value of 17.5 and confirmed the chain mechanism.

For more than two decades, several groups including our group have been engaged in electrophilic organometallic catalysis by using platinum(II) and gold(I) complexes,[91] which gives straightforward access to molecular complexity. While there had been a few reports about the interaction of

Scheme 12. EnT-Initiated Alkylynative Cascade

Lin, Liu and Liu 2023



organic radicals with gold complexes,[92] seminal studies by the Glorius[93] and Toste[94] groups, respectively, in 2013 and 2014, paved the way to a general methodology by showing that an aryl radical generated through reductive photoredox catalysis could add to a gold(I) species. The gold catalysis and the photoredox cycles run cooperatively through electron exchange, promoting the generation of a gold(III) intermediate that undergoes reductive elimination to deliver sp^2−sp^3 cross coupling adducts. This photoredox/gold catalysis merger bypasses the notoriously difficult oxidative addition at gold(I).[95] It relies on the use of easily reduced aryl derivatives, such as aryldiazoniums and iodoniums. Our group checked the versatility of this approach and devised an arylative cyclization of *o*-alkynylphenols **53** with aryldiazonium salts to give benzofuran derivatives.[96]

As an extension, we wished to develop the corresponding alkynylative cyclization to provide 3-alkynyl benzofurans **54**, but haloalkynes such as iodoalkynes **35** are much harder to reduce than aryldiazoniums (respectively, $E \approx -1.5$ and $E \approx -0.2$ V vs SCE), and not surprisingly, the conditions of the previous arylative reaction were not productive. This forced us to devise new reaction conditions as well as to gain insight into the mechanism of this transformation.[85] While it appeared that the presence of light, of a base, and of chloro[tris(para-trifluoromethylphenyl)-phosphine]gold(I) was essential for the reaction to work, we showed that an iridium(III) photocatalyst such as Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ had a strong accelerating effect. After extensive photophysical and theoretical studies, this acceleration could be rationalized by a Dexter EnT[97−99] between the triplet state of the photoexcited iridium photocatalyst and a vinylgold(I) intermediate **55** (Scheme 13). Modeling studies suggested that the vinylgold(I) in its triplet state ^{3}**55** could react with alkynyl iodide **35**, resulting in the formation of intermediate ^{3}**56**, lying 18.5 kcal/mol below the reactants. The intermediate features a lengthening of the C−I bond to 2.12 Å (vs 2.01 Å in the ground state) as well as a severe bending of the C−C−I angle to 115°, a value to be compared with that of the angle of the triplet state ^{3}**35** (I−C−C angle of 129°). These structural features impart a distinctive reactivity to the alkynyl partner. With regard to Xia's report on the photoinduced Sonogashira-type coupling reaction also involving bent alkynyl iodides reacting as "alkynyl radical synthetic equivalent" (Scheme 9),[84] we decided to revisit our preliminary mechanism by postulating the intervention of an energetically accessible alkynyl radical intermediate, which would facilitate a more direct formation of the coupling products **54** via a competitive route to that initially calculated. The modeling, which employed the same calculation level as that previously used,[85] showed a distinct evolution of intermediate complex ^{3}**56**. The latter would fragment to form $I^{\cdot}$ and the Au(II) complex species **57** with an energy cost of 21.2 kcal·mol^{-1}. These two radical species then undergo a rapid recombination process, forming the new intermediate complex **58**. This reaction is highly exothermic with a Gibbs free energy change of 39.4 kcal·mol^{-1} relative to ^{3}**56**. Note that no free alkynyl radical intermediate was found in these calculations.

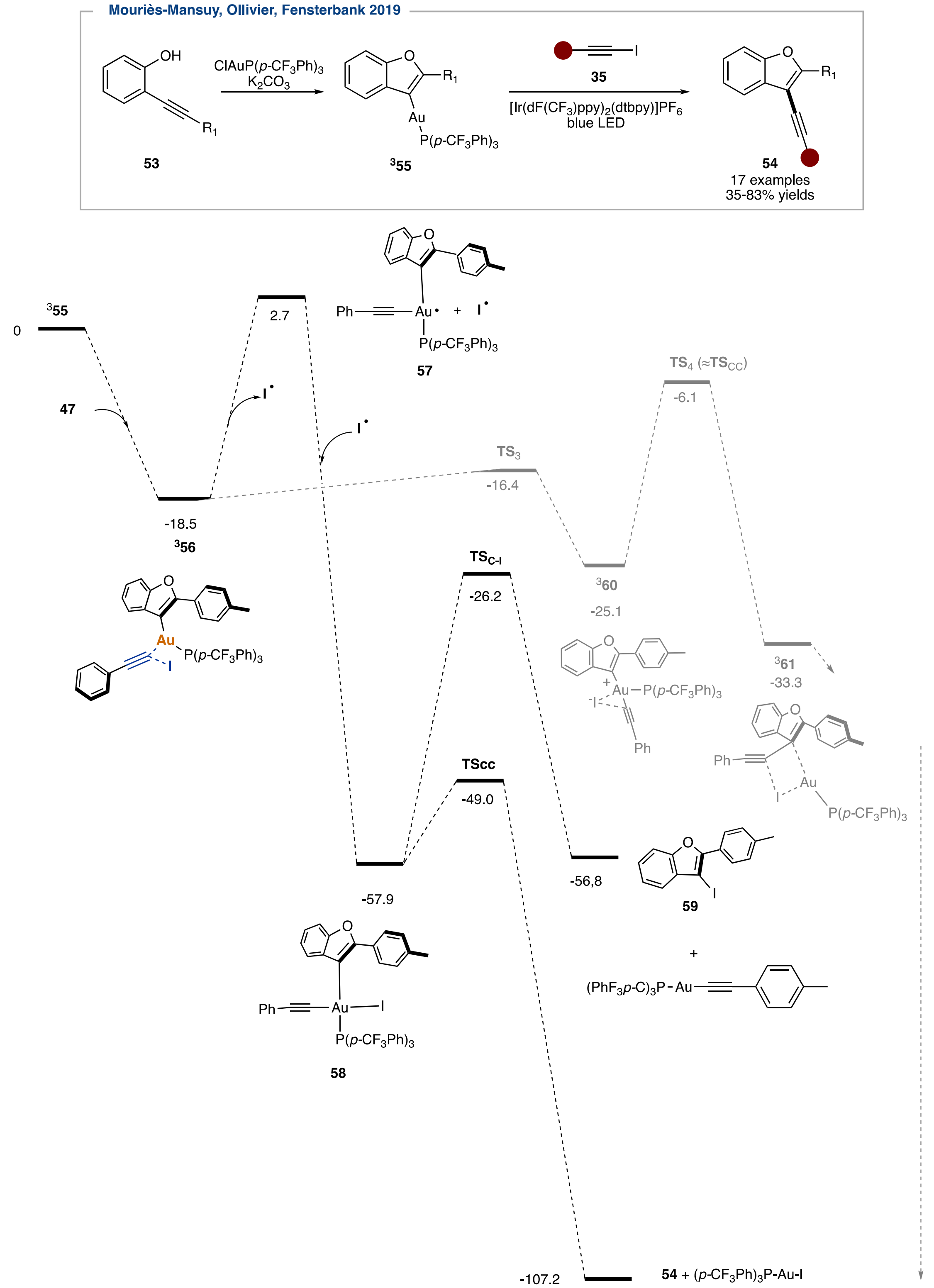
From **58**, we considered two possible sequences: the formation of the C−C bond leading to the desired compound **54** (joined to the formation of L−Au−I), which requires passing through a TS located at 8.9 kcal/mol above **58**, while the formation of a C−I bond results in compound **59** with a TS of 31.7 kcal/mol. This is an unfavorable evolution in comparison to the formation of **54**. These values are in perfect agreement with the experimental results. Although the dissociation of ^{3}**56** into two radicals is more energetic than the formation of the intermediate ^{3}**60** proposed in our previous work, it is noteworthy that, in the radical route, the TScc corresponding to the formation of the key C−C bond is 43 kcal·mol^{-1} lower than the TS4 localized in our first approach (see the SI for details).

This photosensitized oxidative addition of alkynyl iodide **35** has appeared to be quite general as different nucleophiles such as tosylamide **62**[100] or carboxylate anions **64-Cs**[101] could be engaged in the process (Scheme 14). In both cases, the presence of an exogenous photocatalyst is not necessary. In the case of a nitrogen nucleophile, a photoemissive potassium aggregate of tosylamide intermediate **62-K** is formed and serves as an EnT photocatalyst, which triggers the oxidative addition to the corresponding indole gold(I) intermediate. In this study, iodoynamide **35b** bearing a carbamate group was used as an electrophilic partner. Interestingly, this substrate has been only described once by Danheiser who used it as a [2 + 2] cycloaddition partner.[102] This opened access to functionalized indole scaffolds **63**, which could be further transformed thanks to the richness of the alkyne moiety.

In the case of the carboxylate nucleophile **64-Cs**,[101] the absorption spectrum of the corresponding vinylgold(I) intermediate showed a clear bathochromic shift compared to the previously studied vinylgold complexes based on a benzofuran or an indole scaffold so that typical blue LED irradiation guarantees sufficient light activation. Previously undescribed 3-alkynylidenephthalides **65** were readily obtained. Very recently, a modification of reaction conditions proved successful for the alkynylative cyclization of allenoates with iodoalkynes **35**, leading to valuable *β*-alkynyl-*γ*-butenolides.[103] A similar mechanism is presumably at play.

SET Processes. Although, as mentioned above, haloalkynes exhibit relatively low reduction potentials (ca. −1.50 V vs SCE for an iodoalkyne **35**), they have been nevertheless engaged in reaction conditions favoring reductive SET processes. In 1999, an intriguing chromium(II)-mediated alkynylation of benzaldehyde **67** using 1-decynyl(phenyl)iodonium tetrafluoroborate **66** was reported (Scheme 15).[104] Up to 63% yield of propargylalcohol **68** could be obtained, and no phenylation was observed, which is consistent with the high rate of iodobenzene recovery. Nevertheless, these findings did not necessarily converge to the formation of an alkynyl radical as previous reports of SET reduction of alkynylaryl iodonium salts transiting via an iodanyl radical intermediate showed major cleavage of the aryl-iodine bond and the corresponding

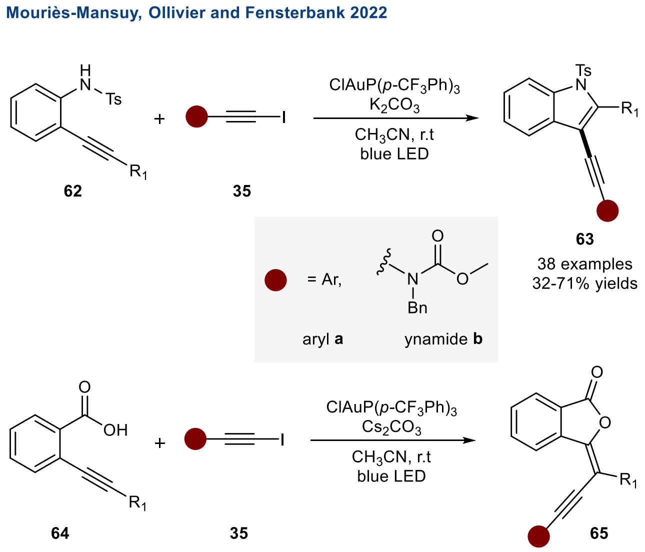
Scheme 13. Modeling Studies for the Photosensitized Gold(I) Catalyzed Alkynylative Cyclization of *o*-Alkylnylphenols: An Alkynyl Radical Based Pathway vs the Nonradical Pathway Proposed Previously[85]



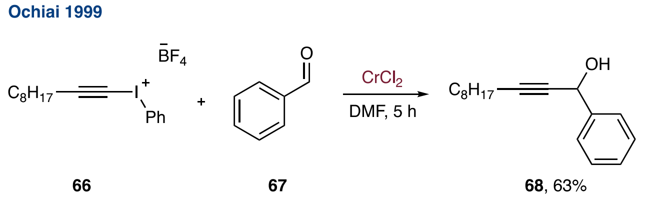
iodoalkynes were recovered.[105] More likely, a nucleophilic alkynyl-Cr(III) species is formed that alkylates benzaldehyde. Overall, this corresponds to an umpolung of the alkynyl moiety initially introduced as an electrophilic iodonium and used as a nucleophilic organometallic intermediate.

The use of alkynylsamarium intermediates has been studied by the group of Kunishima and Tani (Scheme 16).[106] Three routes were developed to access these derivatives, which were reacted with diverse electrophiles such as carbonyl derivatives and activated alkyl halides or acyl halides under Barbier or Grignard conditions. The first route consisted of trans-

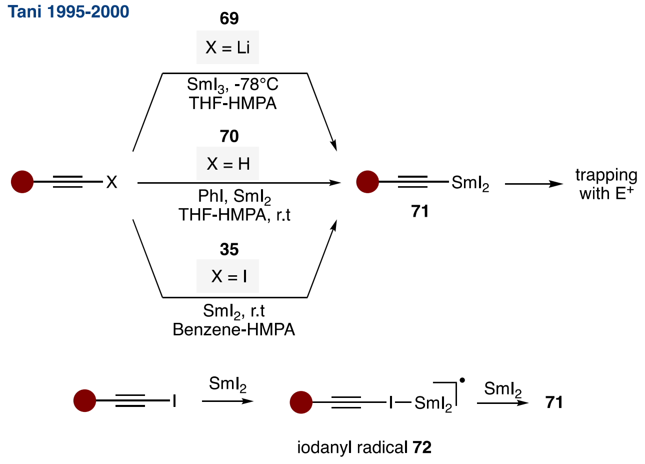
Scheme 14. Synthesis of Alkynylated Indoles via the Photoactivation of in Situ Generated Organogold Species



Scheme 15. Alkynylation of Aldehydes with Alkynyliodonium Salts



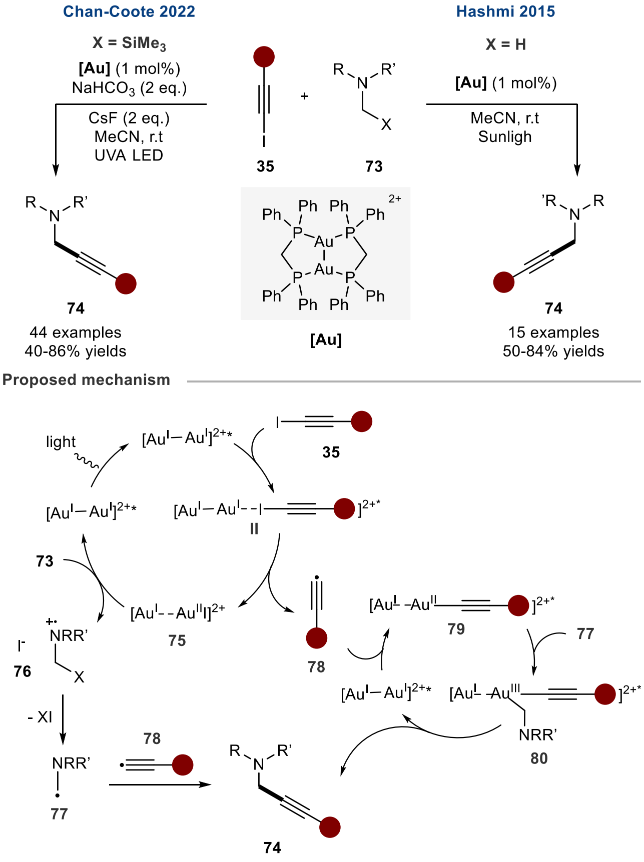
Scheme 16. Alkynylsamariums Reactants



metalation between an alkynyllithium species **69** and SmI_3, the second of the deprotonation of the alkyne **70** by tetrahydrofurylsamarium generated by PhI and SmI_2 in THF, and the third one of the reduction of an alkynyl iodide **35** by SmI2. A solvent dependence was proposed in the mechanism of formation of alkynylsamarium species **71**. In benzene-HMPA, double SET from SmI_2 would lead to **71** via an alkynyl radical. In THF-HMPA, the first SET could lead to an alkynyl radical intermediate that abstracts a hydrogen from THF (HAT reaction). The resulting α-oxygenated radical would be reduced by SmI_2 to generate a carbanion, which could deprotonate the generated alkyne **70**. However, not all the experimental findings secured these hypotheses, and the intervention of a true alkynyl radical remained speculative. The first SET could generate the iodanyl radical intermediate **72** that is further reduced by a second equivalent of SmI_2 to **71**.

SET via Photoredox Processes. Given the hypothesis of alkynyl radical involvement, it makes sense that photoredox conditions have also been used to generate such species to promote alkynylation reactions. In 2015, the group of Hashmi devised a C(sp^3)-H alkynylation of tertiary aliphatic amines **73** with 1-iodoalkynes **35** in the presence of [**Au**] = $[Au_2(dppm)_2](OTf)_2$ (dppm = bis(diphenylphosphino) methane) under sunlight irradiation (Scheme 17).[107] Good yields of propargyl amines **74** were obtained. A mechanistic proposal involving the SET reduction of iodoalkyne **35** by the photoexcited gold complex was provided on the basis of several experimental results. First, there is a good match between the reducing ability of the excited state of $[Au_2(dppm)_2]^{2+}$ (around −1.60 V vs SCE) and the reduction potential of an alkynyl iodide **35** (around −1.50 V vs SCE). Second, minute amounts of alkynes and diynes were also detected in these reactions. Then, digold complex **75** is presumably reduced by the tertiary amine. The resulting aminium **76** would undergo proton loss to generate α-amino radical **77**. Radical−radical coupling[79,80] between the alkynyl radical and the α-amino radical based on the radical persistent effect would form the final adduct **74**.

Scheme 17. Gold-Catalyzed Photoredox Cross-Coupling of Tertiary Alkylamines with Iodoalkynes

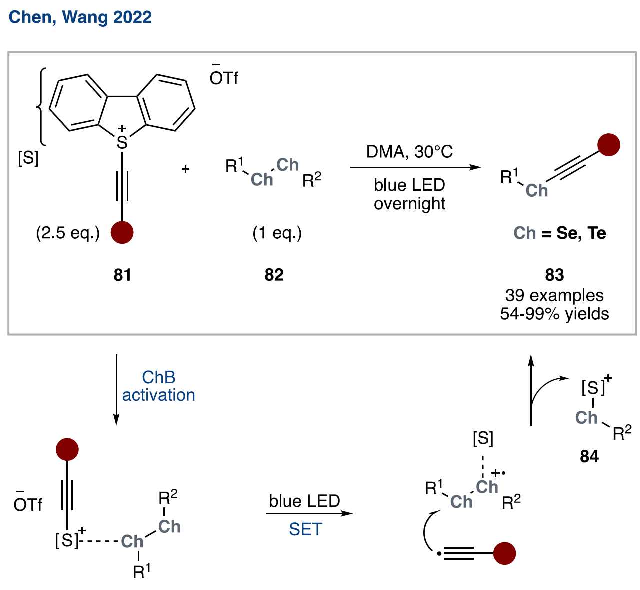


A related alkynylation of tertiary α-silylamine was reported recently by Coote, Chan, and co-workers. Using the same type of dinuclear gold(I) photocatalyst $[Au_2(dppm)_2]Cl_2$ and modified reaction conditions, notably UVA LED irradiation (λ = 365 nm), fair to good yields of propargyl amines were obtained (Scheme 17).[108] A similar oxidative quenching of the excited photocatalyst by iodoalkyne **35** was advanced by the authors. A series of control experiments were achieved to probe the involvement of radical species, notably the formation of a diyne compound in the absence of the amine. Also, kinetic analysis based on Hammett plots showed that the cross-coupling reactions of tertiary α-silylamines **73** ($X = SiMe_3$) with iodoalkynes **35** bearing an electron withdrawing group proceeded more rapidly than those with an electron-donating group. This was consistent with the buildup of negative charge in the transition state of the rate-limiting SET step. Moreover, some extensive DFT calculations supported a mechanism similar to that of Hashmi's but also provided more insight in the key C−C bond formation step. The authors notably highlighted that complex [**Au**] plays a key role in mediating the cross-coupling reaction.

Thus, a gold(III)-catalyzed cross-coupling-type pathway might be operative, involving the sequential trapping of the two radical species **77** and **78** by $[Au_2(\mu\text{-dppm})_2]^{2+}$ to generate the organogold(III) species **80** via **79**. Subsequent reductive elimination produces propargylamine products **74**. This gold mediated C−C bond forming process appeared kinetically and thermodynamically more favorable by DFT than a radical−radical coupling process.

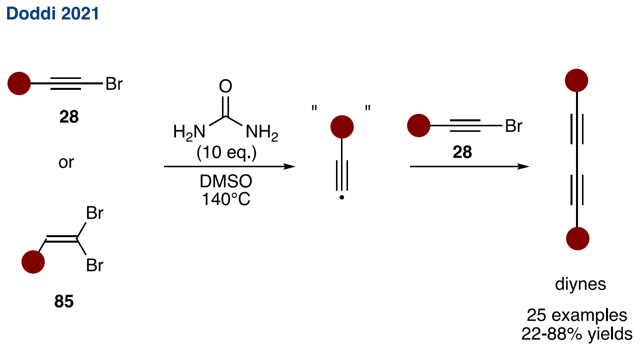
Chalcogen bonding, a noncovalent interaction between an electron-poor chalcogen atom and a Lewis base, has emerged as a significant concept in chemistry, leading to the discovery of many activation modes for multiple processes. Chen, Wang, and co-workers developed a chalcogen bonding (ChB) catalysis strategy using alkynylsulfonium salts **81**, which form photoactive complexes in the presence of electron donor substrates (Scheme 18).[109] DFT calculations and UV−vis spectroscopy confirmed the formation of the photoactive charge transfer complex (CTC) necessary for alkynyl radical generation. Additionally, ^{77}Se NMR experiments revealed an upfield shift of the resonances due to the weak interaction of **82** with the sulfonium salt **81**. Upon irradiation, the alkynylsulfonium salt undergoes photolysis, leading to direct cleavage of the C−S bond via single electron transfer (SET). This process would give rise to an alkynyl radical, which then undergoes selenation and tellurylation reactions. High yields of alkynylated chalcogen product **83** were observed for various functional groups in these transformations. It is worth noting that the resulting chalcogen-sulfonium salt **84** can further react with the alkynyl radical to afford products **83**.

Scheme 18. Chalcogen-Bonding Catalysis for the Generation of Alkynyl Radicals



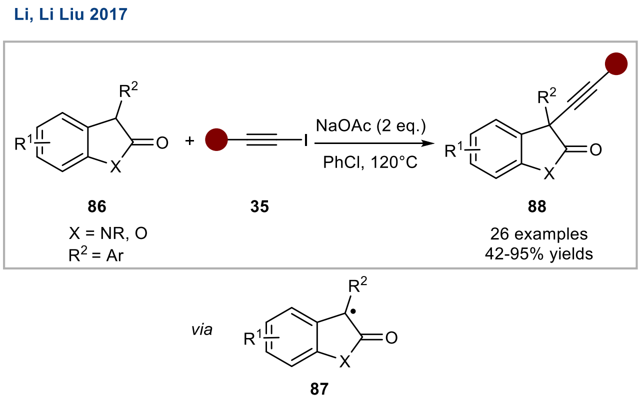
Thermal Processes. Doddi and co-workers reported the use of urea as a catalyst for the generation of alkynyl radicals via a single electron transfer (SET) event under thermal conditions (Scheme 19).[110] They showed that 1,1-dibromoalkenes **85** can be transformed into diynes via a metal-free homolytic alkynyl substitution (HAS). These 1,1-dibromoalkenes **85** served as an in situ source of bromoalkynes **28**, which can also be used directly under these urea-catalyzed conditions. The proposed mechanism would involve an initial SET event from urea, followed by homolytic cleavage of the C−Br bond of bromoalkyne **28** to form an alkynyl radical. This radical then reacts with another molecule of **28** and yields the diyne products after bromine radical elimination. The authors demonstrated the role of urea and that no diyne product could be obtained from a terminal alkyne. Under these conditions, the described HAS process could be extended to disubstituted alkynes.

Scheme 19. Urea Promoted Generation of Alkynyl Radicals



Li, Liu, and co-workers published a novel method for the alkylation of 2-oxindoles **86** without the use of transition-metal catalysts under thermal conditions (Scheme 20).[111] This approach utilizes readily available iodoalkynes **35** and sodium acetate as a base, achieving yields of up to 95% with notable functional group tolerance. The proposed mechanism would

Scheme 20. Alkynylation of 2-Oxindoles through Radical−Radical Coupling



begin with the homolytic cleavage of the C−I bond in the iodoalkynes **35** by thermal activation, generating both alkynyl and iodine radicals. The iodine radical then abstracts a hydrogen atom from 2-oxindoles **86**, producing HI that is subsequently neutralized by the base. The authors proposed that the resulting 2-oxindole radical **87** couples directly with the alkynyl radical to yield the desired product **88**.

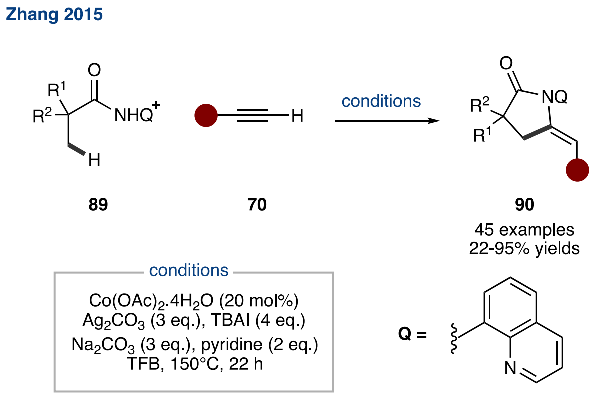
Related to the previously discussed Hashmi's alkynylation of tertiary amines, an iron(II)-catalyzed process in the presence of an excess *tert*-butyl hydroperoxide was also worked out.[112] The key alkynyl radical formation was proposed to take place thermally in MeCN at 120 °C.

Alkyne-H as Precursors

While most reports on alkynyl radical generation utilize some form of activated alkyne source, a few studies have invoked the formation of alkynyl radicals from simple alkyne precursors.

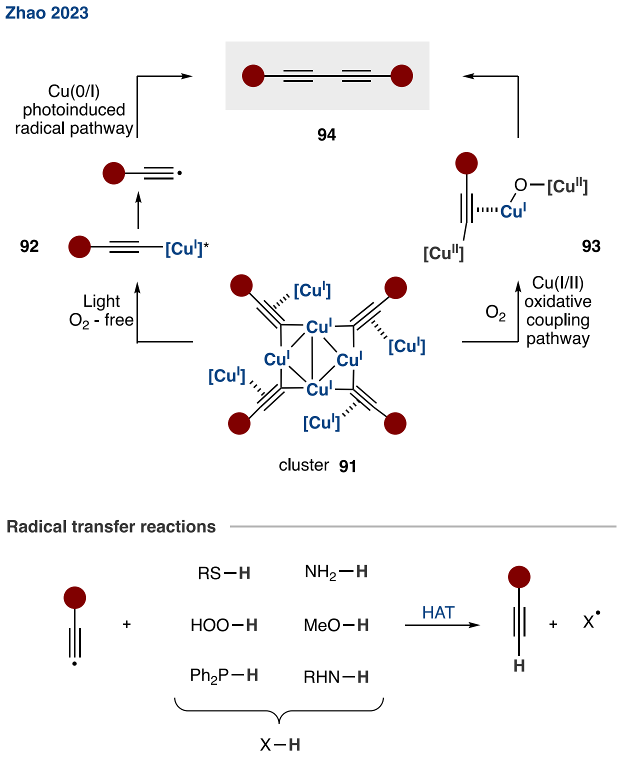
In a study by Zhang and co-workers, a cobalt-catalyzed functionalization of unactivated sp^3 C−H bonds **89** using terminal alkynes **70** as reaction partners for the synthesis of pyrrolidinones **90** was reported (Scheme 21).[113] The reaction requires silver carbonate (Ag_2CO_3) as a cocatalyst and a bidentate directing group, 8-aminoquinolyl (Q), to promote C−H bond activation. An alkynyl radical intermediate was proposed to add on a cobalt(III) intermediate. The resulting cobalt(IV) would undergo reductive elimination to provide products **90**.

Scheme 21. Cobalt Catalyzed Synthesis of Pyrrolidinones from Aliphatic Amides and Terminal Alkynes



Glaser coupling is a well-known reaction that has been extensively studied, although the exact mechanism remains unclear. A recent report by Zhao and Zhang presents a novel approach to this reaction, providing strong evidence for the involvement of two distinct pathways: an aerobic Cu(I/II)-mediated oxidative pathway and an anaerobic, photoinduced Cu(0/I) pathway leading to the formation of highly reactive alkynyl radicals (Scheme 22).[114] In the presence of oxygen, the reaction proceeds through the established oxidative coupling pathway, facilitated by Cu(I) and Cu(II) species. The Cu(I) acetylide complex is oxidized to form a mixed-valence Cu(I/II) species, characterized as a Cu-acetylide/Cu−O merged cluster **93**. Under anaerobic, light-irradiated conditions, Cu(I) acetylides within macrocyclic octanuclear cluster **91** would undergo photoexcitation, generating alkynyl radicals. Alkynyl radical adducts with radical scavengers like TEMPO and 1,1-diphenylethylene were mentioned. When cluster **91** was irradiated in the presence of various X−H substrates (alkynes, amines, alcohols, thiols, and phosphines), HAT reactivity from the alkynyl radical was observed as some DMPO spin-trapping adducts of the resulting radicals were presumably detected by EPR.

Scheme 22. New Mechanism for Glaser Coupling Involving the Formation of Alkynyl Radical



ALKYNYL RADICALS GRAFTING IN MATERIALS SCIENCE

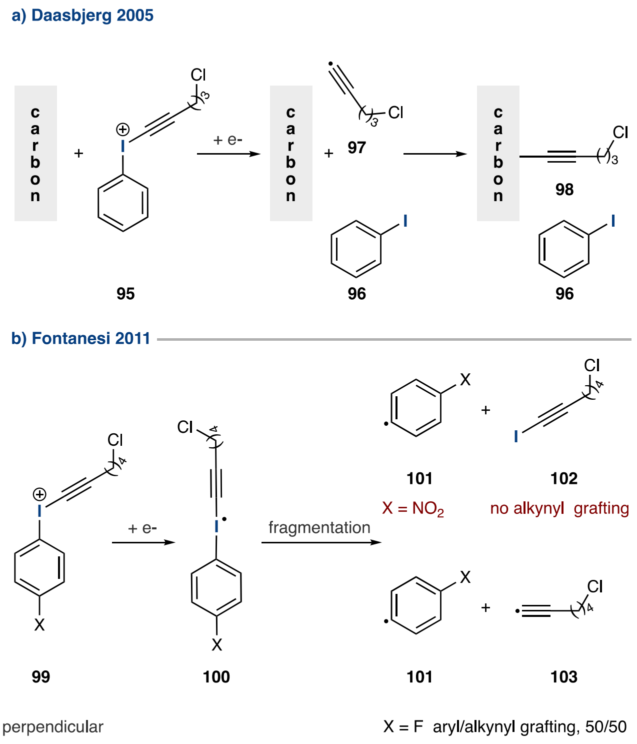
Surface functionalization by C-centered radicals is now a well-established method to access materials with designed properties that can find applications in several domains. The main route followed consisted of using SET processes for the generation of the desired C-centered radical, whether by reductive or oxidative processes.

Reductive SET Processes

The most typical example of radical grafting that springs to mind is the grafting of aryl radicals through the reduction, in most cases electrochemical, of easily reducible aryldiazonium derivatives, as pioneered by Pinson.[115,116] Substrates can be carbon,[117] metals,[118] or Si(111) semiconductors.[119] Aryl radicals could also be grafted from aryliodoniums, even if they require slightly more negative potential (Ep = −0.6 to −0.7 V/SCE) than diazoniums (Ep = 0 to −0.1 V/SCE).[115] The latter also offer the possibility of grafting alkyl, vinyl, and even alkynyl groups. The first example of such alkynyl radical grafting was accomplished by Pedersen, Daasbjerg, and co-workers on glassy carbon surfaces (Scheme 23a).[120] In this report, it is shown that the electrochemical reduction of 5-chloro-1-pentynyl(phenyl)-iodonium tetrafluoroborate **95** (Ep = −0.65 V vs SCE) leads to a great extent to alkynyl radical **97** grafting **98** as deduced by the detection of iodobenzene **96** as the main formed product (wave of iodobenzene at −2.4 V vs SCE) and the observation of chlorine by XPS of the grafted material.

These seminal findings were confirmed by the Baranton group as (1-bromobut-4-yne) and (1-chlorohex-6-yne)-phenyliodo-

Scheme 23. (a) Grafting of Alkynyl Radicals on Carbon Surfaces; (b) Electrochemical Reduction of Alkynyliodonium Salt for the Synthesis of Alkynyl Radicals



nium could also serve as selective sources of alkynyl radicals in electrochemical reduction conditions on divers carbon substrates.[121] Nevertheless, a low coverage of the alkynyl moieties on the surfaces was observed. To rationalize these findings, the dissociation of (1-chlorohex-6-yne)-aryliodonium radicals **100** was modeled by an *ab initio* dynamic reaction coordinate (DRC) approach (Scheme 23b).[122] Upon electron capture, the perpendicular iodonium cations **99** evolve to a planar structure that readily fragments. In the case of an *p*-NO_2-aryl derivative, only grafting of the aryl moiety on the electrode surface was observed. In contrast, a 1:1 aryl/alkynyl grafting ratio was found for the *p*-F compound. These findings were fully consistent with the experimental results.

Oxidative SET Processes

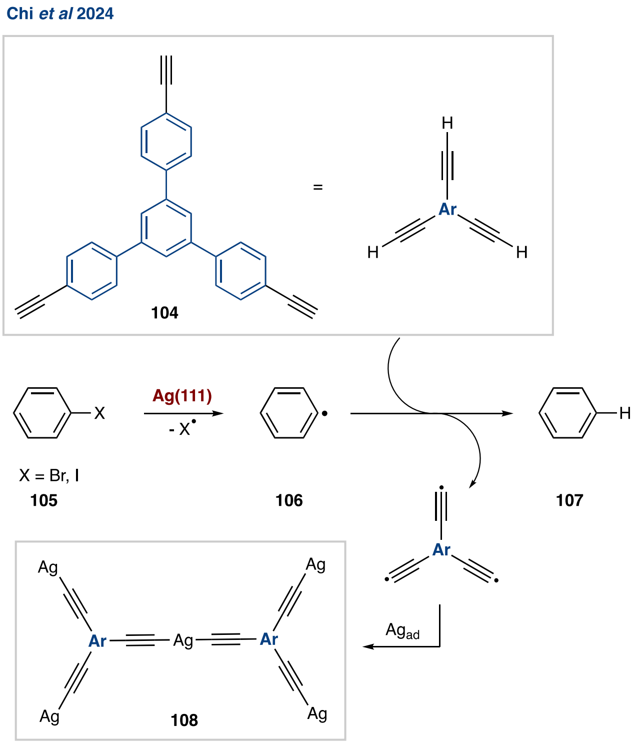
Anodic oxidation of acetylide carbanions can be considered as a mirror process of the previously described cathodic reduction. Based on encouraging thermodynamics, since the reported anodic potential of lithiophenylacetylene, PhCCLi, is approximately 1.0 V vs aqueous Ag/AgCl,[123] Geiger and co-workers studied the oxidation of lithium acetylides as a general pathway for grafting alkynes on glassy carbon electrodes.[124,125]

The direct oxidation of the H-terminated alkyne has also been considered based on the principle that the radical cation originating from the oxidation ($E > 2.0$ V) would lose its proton and generate an alkynyl radical.[126] This was evidenced through the anodic oxidative attachment of ethynylferrocenes to carbon electrode surfaces. The oxidation of either the H-ethynylferrocene or the lithium-acetylide ferrocene was also examined by DFT and revealed the removal of an electron from a mixed ethynyl-ferrocenyl HOMO to generate a ferrocenium-like monocation for both systems, which then evolves through the loss of H^+ or Li^+ with concomitant formation of the alkynyl radical.

HAT Pathway

Very recently, an intermolecular HAT reaction on metal surfaces has been reported.[127] More precisely, phenyl radicals are generated by thermally activating the C−X bond scission of bromo- or iodobenzene **105** on Ag(111) (Scheme 24). These somehow surface-stabilized radicals engage in a HAT process from H-alkyne substrate **104**. The resulting alkynyl radical adds to Ag adatoms and forms alkynyl-Ag-alkynyl structures **108**. This type of reaction pathway proved relatively general with different surfaces notably Cu(111) and alkyne substrates and was supported by scanning tunneling microscopy (STM), temperature-programmed desorption (TPD), and temperature-programmed X-ray photoelectron spectroscopy (TPXPS) studies as well as extensive DFT calculations.

Scheme 24. Intermolecular HAT Reaction on Metal Surface

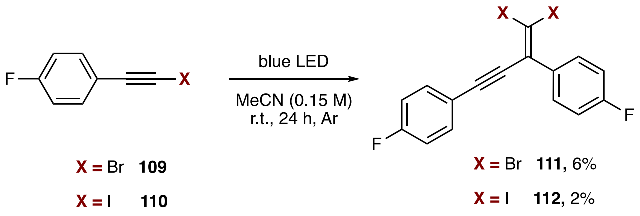


REEVALUATING ALKYNYL RADICAL FORMATION IN SOLUTION: ALTERNATIVE MECHANISMS AND IMPLICATIONS

As we have just seen, a large number of articles report the intervention of an alkynyl radical to lead to alkynylation products, but no tangible evidence of the formation of such an intermediate is provided. This is all the more worrying given that, in a number of cases, alternative mechanisms, notably based on a SOMOphilic process, appear very possible. Other reports refer to the detection of alkynyl radical adducts to support their proposed mechanisms, but such experimental evidence often suffers from methodological or interpretation flaws. Let us examine this in more detail.

First, most of the reactions described involve the photolysis of a haloalkyne. It is important to note that λ_{max} of these derivatives is generally below 280 nm,[100] so irradiation with a blue LED, generally with an emission peak around 450 nm, is probably not very effective in breaking homolytically this C−X bond. We conducted experiments in similar conditions to our previous studies[85,100,101] to verify this hypothesis (Scheme 25). The reactions were performed on 0.15 mmol scale, and all reported yields were determined by ^{19}F NMR using 4,4-difluorobenzophenone as internal standard. The irradiation of both bromoalkyne **109** and iodoalkyne **110** with blue LEDs (1.1 W) in acetonitrile solution over a period of 24 h showed almost no conversion and resulted in the very minor formation of 1,1-dihalo-1-en-3-yne products **111** (6%) and **112** (2%), whose mechanism of formation is discussed below. This observation warrants careful consideration; however, as the term "blue LEDs" encompasses in the literature various experimental setups using lamps of widely differing intensities, it remains conceivable that certain experimental conditions could indeed lead to formation of the alkynyl radical.

Scheme 25. Experimental Results on the Blue LED Irradiation of Haloalkynes



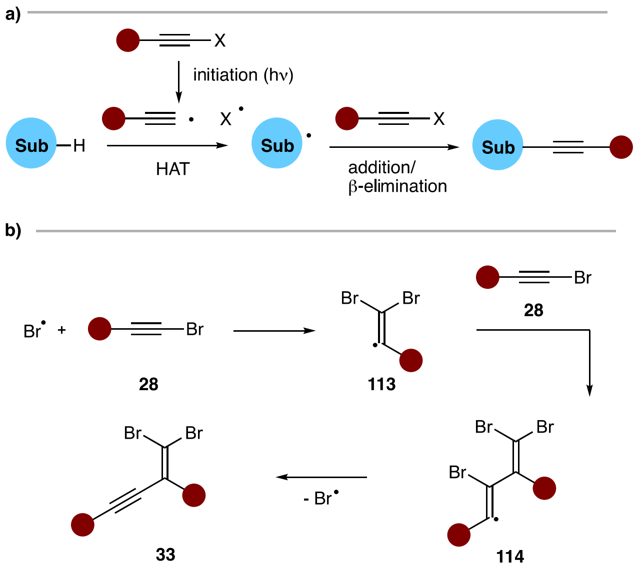
Second, in the case of a proposed alkynyl-X homolytic cleavage by photocatalysis, whether by SET or by EnT, quenching of the photocatalyst luminescence by the iodoalkyne must be established. This was for instance accomplished with the quenching of the excited state of 4CzIPN by an alkynyl triflone **48** of Scheme 12.[90]

Third, although there are no kinetic studies of the HAT process from an alkynyl radical, it seems unlikely that it can be made to react primarily with the substrate if it is in solution in a solvent possessing labile hydrogens with a low BDE, such as THF or toluene. In other words, in such solvents, the reaction of an alkynyl radical will take place with the solvent. In the case of aromatic solvents as reactants, Tiecco's work[76] shows that addition is the major pathway and follows polar effects. The richer the aromatic partner, the more efficient is the addition. In the case of toluene and xylenes, the formation of benzylic radicals is mentioned, which is consistent with this discussion. Therefore, the use of a solvent like MeCN with nonhydridic hydrogens of high BDE should be favored.

Fourth, chain SOMOphilic processes are certainly the path followed in many cases, and they could be initiated by HAT from both minor amounts of the alkynyl radical and/or the X radical originating from the alkynyl-X bond (Scheme 26a).[128,129] Similarly, the formation of 1,1-dibromo-1-en-3-yne products **33**[81,83] could be rationalized by a bromine radical formed in an initiation step that attacks an alkynyl bromide molecule, forming a dibromovinyl radical (Scheme 26b). This vinyl radical could add to another molecule of alkynyl bromide and gives the final product after a subsequent bromine radical β-elimination.

Fifth, the authentication of the intervention of an alkynyl radical through the characterization of spin-trapping adducts is a key question. While the direct EPR of alkynyl radicals could be achieved in 4 K matrixes,[28,39] in solution, only adducts with the DMPO nitrone have been reported. Although the EPR spectra of these spin-trapping adducts are consistent with the formation of a nitroxide radical they cannot be conclusive about the nature of the C fragment added. TEMPO-trapping adducts have been mentioned in a few articles but only one gives a proper HRMS analysis.[92] Note that there is no other characterization of this adduct, which must be difficult to isolate, because of the fragile NO-alkynyl bond.

Scheme 26. (a) Alternative SOMOphilic Pathway; (b) Alternative Mechanism for the Formation of 1,1-Dibromo-1-en-3-yne Products



Finally, it appears that there remains little evidence of free alkynyl radicals reacting in productive C−C bond forming steps except with an aromatic solvent or with the surface of a heterogeneous material. An attractive alternative is probably to use an alkynyl radical synthetic equivalent generated by direct irradiation as shown by Xia[84] or by photosensitization as shown by us.[85,100,101,103] One may also wonder whether such photosensitization is not involved in the previously discussed Rh(I)[86,88] and in the [Au$_2$(dppm)$_2$]Cl$_2$[107,108] catalyzed alkynylation reactions.

CONCLUSIONS

In conclusion, the main aim of this Perspective was to build up an unprecedented body of useful knowledge on the alkynyl radical, which has remained a species largely absent from the repertoire of synthetic intermediates that can be mobilized in interesting ways. While the communities of gas-phase reactivity and materials electrografting have accumulated a number of important insights and methodologies, the synthetic organic chemistry community has clearly lagged behind in this area. However, the rate of publications mentioning an alkynyl radical as an intermediate has suddenly accelerated. Starting from classical methods of photochemical UV irradiation or the use of stoichiometric reagents for reductive SET, current methods based mainly on photocatalysis (redox or EnT) have enabled diverse transformations to occur under milder conditions with functionalized substrates. However, a number of these alkynylation processes are probably not based on a true alkynyl radical, and there are many gray areas, probably due to the fact that the alkynyl radical is particularly difficult to authenticate in the condensed phase. At this stage, the emerging alkynyl radical synthetic equivalent approach by photoactivation appears to be a very promising direction and should contribute to important synthetic developments.

Overall, it is best to keep a cool head about all the hype surrounding the alkynyl radical and bear in mind all the limitations outlined in the previous section. This milestone report should prove particularly useful to the synthetic chemist in developing new reactions that introduce the valuable alkyne motif in complex molecule synthesis, materials chemistry, or biology.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.4c01040.

Theoretical details and Cartesian coordinates for all intermediates and TS (PDF)

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